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Low-grade inflammation and muscular fitness on insulin resistance in adolescents: Results from LabMed Physical Activity Study

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Abstract
Background: Low muscular fitness (MF) and low-grade inflammation has been linked to insulin resistance (IR). Objective: To evaluate the associations between MF and a clustered score of inflammatory biomarkers on IR and to investigate the combined impact of MF and inflammation on IR in adolescents. Methods: This is a cross-sectional analysis with 529 adolescents (267 girls) aged 12 to 18 years. Pubertal stage, socioeconomic status, adherence to the Mediterranean diet, cardiorespiratory fitness, and waist circumference were assessed. Standing long-jump and isometric handgrip dynamometry were used as indicators of MF. Continuous score of clustered inflammatory biomarkers (InflaScore) (sum of Z-scores of C-reactive protein, C3, C4, fibrinogen, and leptin) and IR (homeostasis model assessment of insulin resistance [HOMA-IR] estimated from fasting serum insulin and glucose) were assessed. Results: HOMA-IR and fasting insulin were positively associated with InflaScore and negatively associated with MF, independently of age, sex, pubertal stage, socioeconomic status, adherence to the Mediterranean diet, cardiorespiratory fitness, and waist circumference. Adolescents classified as High InflaScore/Unfit showed significantly higher HOMA-IR when compared than those with High InflaScore/Fit and those with Low InflaScore/Fit (F(3,519) = 4.761, P < .003), after adjustments for potential confounders. Unfit adolescents with high InflaScore had the highest odds of expressing high HOMA-IR (odds ratio, OR = 2.40, 95% confidence interval [CI]: 1.2-5.6) and insulin risk (2.53 95% CI, 1.5-5.9) when compared to those of the Low InflaScore/ Fit group, after adjustments for potential confounders. Conclusion: Higher levels of MF seem to minimize the deleterious effect of inflammation on IR.
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Conclusion: Higher levels of MF seem to minimize the deleterious effect of inflammation on IR.

KEYWORDS
handgrip, inflammation, insulin resistance, strength, youth

1 INTRODUCTION

Insulin resistance (IR) is a reduced physiological response of the peripheral tissues, such as the adipocytes, liver, and skeletal muscle, to normal levels of insulin. The skeletal muscle is the predominant site of insulin-mediated glucose uptake in the postprandial state, and skeletal muscle IR is considered the initiating or primary defect of IR that is evident decades before β-cell failure and overt hyperglycemia develops. A recent systematic review has shown that the prevalence of IR in youth is associated with a chronic state of low-grade inflammation.

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inflammation. A chronic low-grade inflammation and an activation of the immune system are involved in the pathogenesis of atherosclerosis, obesity-related IR, and type 2 diabetes. Although the concept of type 2 diabetes as an inflammatory disease has recently emerged in the literature, there is a growing body of evidence supporting its definition/classification.

Presently, there is a growing interest on the health benefits of a healthy skeletal muscle. Muscular fitness (MF) has been recognized as an important component in the pathogenesis and prevention of chronic diseases and is inversely and independently associated with all-cause mortality. Several studies in adolescents showed that MF is negatively associated with markers of IR and low-grade inflammation.

The skeletal muscle is a highly energetic tissue that contributes substantially to basal metabolic rate and acts as an endocrine organ expressing and releasing several cytokines in response to muscle contractions. Given that skeletal muscle is the largest organ in the human body and low-grade inflammation has been linked to IR, it is of public health interest to better understand whether the combined impact of MF and inflammation affects insulin metabolism. To our knowledge, there are no studies examining the combined association of MF and low-grade inflammation on IR, in adolescents.

The purpose of this study was 2-fold: (1) to explore the associations between MF and a clustered score of inflammatory biomarkers with IR parameters and (2) to investigate the combined impact of MF and a clustered score of inflammatory biomarkers on IR, in adolescents.

2 | METHODS

2.1 | Study design and sample

This report is part of the Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity (LabMed Physical Activity Study), a school-based, prospective cohort study carried out in 4 Portuguese cities from the North Region. Detailed description of sampling and recruitment approaches, data collection, and analysis strategies has been described elsewhere. In short, baseline data were collected in the fall of 2011, for 1229 apparently healthy adolescents, that is, participants without any medical diagnosis of physical or mental impairment, (aged 12 to 18 years). Of the 1229 adolescents who agreed to participate in the LabMed study, 534 accepted to undergo blood collection. Five adolescents were excluded due to hs-CRP values >10 mg/L, which may be indicative of acute inflammation or illness. Thus, leaving 529 adolescents (267 girls, 262 boys, mean age 14.3 ± 1.7 years) as the final sample for this report.

The LabMed Physical Activity Study was conducted in accordance with the Helsinki Declaration for Human Studies and approved by the Portuguese Data Protection Authority (#1112434/2011) and the Portuguese Ministry of Science and Education (0246200001/2011). All participants were informed of the study’s goals, and written informed consent was obtained from participating adolescents and their parents or legal guardians.

3 | MEASURES

3.1 | Muscular fitness

3.1.1 | Handgrip strength

Upper body isometric strength (handgrip strength test) was assessed using a handgrip dynamometer (T.K.K. 5001, Grip-A, Takei, Japan), adjusted by sex and hand size for each adolescent. The participants were instructed to stand with their arms completely extended, squeezing gradually and continuously the handgrip up to the maximum of their strength, for at least 2 seconds, performing the test twice alternating with both hands. The best score for each hand was recorded in kilograms. The handgrip score (kg) was calculated as the average of the left and right and then expressed per kilogram of body weight.

3.1.2 | Standing long-jump test

Lower body explosive strength (standing long-jump test) was performed in an indoor wood floor gymnasium and the adolescents were instructed to jump from the starting line and to push off vigorously and jump as far forward as possible landing on both feet and staying upright. The test was done twice, and the best attempt was recorded. The standing long-jump score was determined by the distance between the last heel-mark and the take-off line.

The results of the handgrip strength and standing long jump tests were transformed into standardized values ([Z-score = (participant’s value−mean value of the sample)/standard deviation], by age and sex. Then, the sum of the Z-scores of the 2 tests was performed to create the MF score.

3.2 | Blood sampling

Blood samples were obtained from each subject early in the morning, following a 10-hour overnight fast by venipuncture from the ante-cubital vein. The samples were stored in sterile blood collection tubes in refrigerated conditions (4 °C to 8 °C) for no longer than 4 hours during the morning of collection and then sent to an analytical laboratory for testing according to standardized procedures, as follows: glucose, Hexokinase method (Siemens Advia 1600/1800 Erlangen, Germany); insulin, chemiluminescence immunoassay (Siemens ACS Centaur System, Erlangen, Germany); hs-C-Reactive Protein, latex enhanced immunoturbidimetric assay (Siemens Advia 1600/1800 Erlangen, Germany); Fibrinogen, Clauss method (Siemens BCS System, Erlangen, Germany); Complement factors C3 and C4, Immunoturbidimetric assay (Siemens Advia 1600/1800, Erlangen, German). Leptin, hs-C-Reactive Protein, C3, and C4 were determined in serum and fibrinogen was determined in plasma. All assays were performed in duplicate according to the manufacturers’ instructions.

3.3 | Insulin resistance

The homeostatic model assessment (HOMA-IR), calculated as the product of basal glucose (mmol/L) and insulin (μIU/mL) levels divided by 22.5, was used as a proxy measure of IR.
3.4 | Anthropometrics

Body height was measured to the nearest 0.1 cm in bare or stocking feet with the adolescent standing upright against a portable stadiometer (Seca 213, Hamburg, Germany). Body weight was measured to the nearest 0.10 kg with the participant lightly dressed using a portable electronic weight scale (Tanita Inner Scan BC 532, Tokyo, Japan).Waist circumference measurements were taken in a standing position, to the nearest 0.1 cm, with a tape measure midway between the lower rib margin and the anterior superior iliac spine at the end of normal expiration.

3.5 | Pubertal stage

Participants self-assessed their pubertal stage of secondary sex characteristics (breast and pubic hair development for girls, genital, and pubic hair development for boys; ranging from stages I to V), according to the criteria of Tanner and Whitehouse.

3.6 | Socioeconomic status

The socioeconomic status was assessed with the Family Affluence Scale, developed specifically to measure children and adolescents socioeconomic status in the context of the Health Behaviour in School-Aged Children Study.

3.7 | Adherence to the Mediterranean diet

To assess the degree of adherence to the Mediterranean diet, the KIDMED index (Mediterranean Diet Quality Index for children and adolescents) was used. Briefly, the index is based on a 16-questions self-administered, which sustain the principles of the Mediterranean dietary patterns, as well as, those that undermine it. The results of index varied between 0 and 12 points. The questions that have 1 negative connotation in relation to Mediterranean diet were equal to (-1), the questions that constitute positive aspect were equal to (+1).

3.8 | Cardiorespiratory fitness

Cardiorespiratory fitness was assessed with the 20-m Shuttle Run Test (20-m SRT). The test was performed according to the standardized protocol and the detailed description of this test can be found elsewhere. We estimated the maximum oxygen consumption \( \dot{V}_{O2\text{max}} \) (mL/kg/min) from the 20-m SRT number of laps performed using the Leger et al' equation (24).

3.9 | Data management

As previously published elsewhere, we computed a continuous score of clustered inflammatory biomarkers (InflaScore) summing the Z-scores by age and sex from C-Reactive Protein, C3, C4, leptin, and fibrinogen. High-risk group was defined as the first tertile and low-risk group as the second and third tertiles. Glucose, insulin, and HOMA-IR were transformed to standardized values \( Z = \frac{X - \mu}{\sigma} \) by age and sex. High risk (at risk) was considered when the individual had \( \geq 1 \text{SD} \) (standard deviation) of this Z-score as previously suggested.

According to the MF score, participants were divided into 2 groups: Unfit (first tertile) and Fit groups (second and third tertiles). Then, according to the InflaScore groups (High InflaScore and Low InflaScore) and MF group (Unfit and Fit), 4 exclusive groups were created: (1) Low InflaScore/Fit; (2) Low InflaScore/Unfit; (3) High InflaScore/Fit, and (4) High InflaScore/Unfit.

4 | STATISTICAL ANALYSIS

Descriptive data are presented as means and SD. For MF tests, HOMA-IR and each biomarker a Z-score was computed by age and sex. One-way ANOVA with Bonferroni posthoc multiple comparison tests were performed to assess mean differences across 4 groups of MF for continuous variables and chi-square for categorical variables.

Linear regression models were performed to determine the associations between the IR parameters (as the dependent variables) and MF score or InflaScore (as predictor variables). We performed 2 different models; Model 1 Unadjusted model; and Model 2: adjusted for age, sex, pubertal stage, adherence to the Mediterranean diet, socioeconomic status, cardiorespiratory fitness, and waist circumference. Standardized regression coefficients were used to express the \( \beta \) in the linear regression analyses.

Analysis of covariance (ANCOVA) with Bonferroni posthoc multiple comparison tests was used to assess the differences between mean values of HOMA-IR, (\( Z \)-score by age and sex) across groups of InflaScore (High vs Low) stratified according to different levels of MF (Unfit and Fit). Covariates included were age, sex, pubertal stage, adherence to a Mediterranean dietary pattern (KIDMED index), socioeconomic status, cardiorespiratory fitness, and waist circumference.

Binary logistic regression models were constructed to verify the relationship between the combined associations of MF and InflaScore and high risk of IR parameters, adjusted for age, sex, pubertal stage, adherence to a Mediterranean dietary pattern, socioeconomic status, cardiorespiratory fitness, and waist circumference.

Data analysis was performed using the Statistical Package for the Social Sciences for Windows (Version 21.0 SPSS Inc., Chicago, Illinois). A P value \(< .05\) denoted statistical significance.

5 | RESULTS

Descriptive characteristics of the participants are presented in Table 1. Adolescents classified as High InflaScore/Unfit presented the worst cardiometabolic profile, having higher weight and higher waist circumference and lower cardiometabolic fitness values then other all the 3 groups \( P < .05\) for all.

Regression analysis (Table 2) showed a significant positive association of InflaScore with HOMA-IR (Standardized \( \beta = .153; P < .001\) and insulin (Standardized \( \beta = .333; P < .001\). In addition, MF score was inversely associated with HOMA-IR (Standardized \( \beta = -.112; P < .029\)) and insulin (Standardized \( \beta = -.122; P < .016\) after adjustments for potential confounders.
Data are mean and standard deviations. HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; C3 and C4, complement factors; CRF, cardiorespiratory fitness.

After adjustments for potential confounders.

HOMA-IR, homeostasis model assessment of insulin resistance. Model 1: Unadjusted model. Model 2: Analysis adjusted for age, sex, pubertal stage, socioeconomic status, adherence to a Mediterranean diet, cardiorespiratory fitness, and waist circumference; (2) adolescents with High InflaScore/Unfit had the highest odds of expressing high HOMA-IR and insulin when compared to those of the Low InflaScore/Fit group.

Collectively, these findings suggest that a combined effect of unhealthy MF in the presence of a high inflammatory profile seems to increase the IR risk in adolescents.

There is growing evidence suggesting that the systemic low-grade inflammation is closely connected to the IR and type 2 diabetes. The hypothesis that low-grade inflammation is causally linked to IR is supported by clinical evidence on correlations between inflammatory markers and measures of IR.

Table 3 shows the results of the study indicate that 1) MF was inversely and InflaScore was positively associated with IR after adjustments for potential confounders, such as age, sex, pubertal stage, socioeconomic status, adherence to a Mediterranean diet, cardiorespiratory fitness, and waist circumference; 2) adolescents with High InflaScore/Unfit had the highest odds of expressing high HOMA-IR and insulin when compared to those of the Low InflaScore/Fit group.

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6 | DISCUSSION

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reductions in the concentrations of CRP, IL-6, and fibrinogen were observed with negligible changes in body weight and/or BMI, however with a significant decrease in HOMA-IR. The mechanism for which inflammation affects the IR is not fully understood; however, it seems that inflammatory cytokines can affect insulin signaling at the molecular level and similar molecular events may also affect β-cell function.27

Increasing evidence suggests that MF is an emerging predictor for cardiovascular disease mortality, independently of several risk factors, such as hypertension, obesity, smoking, and cardiorespiratory fitness.4,27-29 Adipocytes within the visceral fat depot show substantially higher fatty acid fluxes than superficial subcutaneous adipocytes and is characterized by higher secretion of pro-inflammatory cytokines and lower secretion of the anti-inflammatory adipokine.27 Importantly for this discussion, our results remained significant even after a fatness parameter (ie, waist circumference) was additionally included as a confounder variable in our analyses.

The findings of our study also support the current physical activity guidelines for children and adolescents which recommends regular engagement in muscle-strengthening activities due to its health-related benefits, including the prevention for cardiometabolic risk factors.31 The data from our aforementioned results guide us to agree with the suggestion that MF could be considered as a general index of MF in youth.32 The relationship between inflammatory biomarkers and MF on IR in youth has been previously described;13,14,33 however, our results built upon the previous research by showing that adolescents with an adverse inflammatory profile and unhealthy MF may be at increased the risk of IR, independently of other several potential confounders. Given the modifiable nature of MF status and the growing imperative of the global epidemic of the type 2 diabetes,

![Figure 1](image-url)

**Figure 1** Homeostasis model assessment of insulin resistance across inflammatory clustered score profile groups (low risk and high risk) by muscular fitness groups (low vs high). Bars represent adjusted means and 95% confidence intervals, for age, sex, pubertal stage, adherence to a Mediterranean dietary pattern, socioeconomic status, cardiorespiratory fitness, and waist circumference as confounders.

![Table 3](table-url)

**Table 3** OR of high HOMA-IR, insulin, and glucose by muscular fitness and inflammatory profile categories

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High HOMA-IR $^a$</th>
<th>OR unadjusted (95% CI)</th>
<th>P value</th>
<th>OR adjusted (95% CI) $^b$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low InflaScore/Fit</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low InflaScore/Unfit</td>
<td>2.70 (1.3-5.9)</td>
<td>.008</td>
<td>1.76 (0.7-3.8)</td>
<td>.172</td>
<td></td>
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<tr>
<td>High InflaScore/Fit</td>
<td>2.30 (1.05-5.1)</td>
<td>.036</td>
<td>1.58 (0.6-3.7)</td>
<td>.280</td>
<td></td>
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<tr>
<td>High InflaScore/ Unfit</td>
<td>7.01 (3.5-13.8)</td>
<td>&lt;.001</td>
<td>2.40 (1.2-5.6)</td>
<td>.040</td>
<td></td>
</tr>
<tr>
<td>High insulin $^a$</td>
<td>Low InflaScore/Fit</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low InflaScore/Unfit</td>
<td>1.85 (0.8-4.1)</td>
<td>.126</td>
<td>1.10 (0.5-2.6)</td>
<td>.823</td>
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<tr>
<td>High InflaScore/Fit</td>
<td>2.25 (1.05-5.1)</td>
<td>.036</td>
<td>1.40 (0.6-3.3)</td>
<td>.421</td>
<td></td>
</tr>
<tr>
<td>High InflaScore/ Unfit</td>
<td>8.00 (4.12-15.3)</td>
<td>&lt;.001</td>
<td>2.53 (1.5-5.9)</td>
<td>.031</td>
<td></td>
</tr>
<tr>
<td>High glucose $^a$</td>
<td>Low InflaScore/Fit</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low InflaScore/Unfit</td>
<td>2.70 (0.6-2.3)</td>
<td>.491</td>
<td>1.26 (0.6-2.5)</td>
<td>.489</td>
<td></td>
</tr>
<tr>
<td>High InflaScore/Fit</td>
<td>2.30 (0.45-1.9)</td>
<td>.965</td>
<td>0.99 (0.4-2.0)</td>
<td>.987</td>
<td></td>
</tr>
<tr>
<td>High InflaScore/ Unfit</td>
<td>7.01 (0.47-1.8)</td>
<td>.945</td>
<td>1.03 (0.4-2.4)</td>
<td>.937</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence intervals; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratios; 1, reference category.

$^a$ Transformed to standardized values (Z-score = [participant’s value – mean value of the sample]/standard deviation) by age and sex. High risk (at risk) was considered when the individual had ≥1SD of this Z-score.

$^b$ Adjusted for age, sex, pubertal stage, socioeconomic status, and adherence to the Mediterranean diet, cardiorespiratory fitness, and waist circumference.
intervention studies are of importance to determine the effectiveness of evidence-based strategies, specifically targeted at improvements in muscular strength in children and adolescents in different metabolic phenotypes. These findings call for further investigation.

The strengths of our study include the inclusion of important confounding variables such as adherence to a Mediterranean diet, a predictor of cardiometabolic health and IR,34 fatness, and cardiorespiratory fitness35 and the standardized use of different components of MF and inflammatory biomarkers.

This study is subject to certain limitations. First, owing to its cross-sectional design, we cannot infer that our observed associations reflect causal relationships. Second, blood samples only reflect inflammation and IR at a specific time point. Nonetheless, we measured several inflammatory biomarkers, which provided us with a more comprehensive assessment of the inflammatory status of our sample, since we did not rely on only a single marker. In addition, a composite continuum score of inflammatory biomarkers is becoming widely recognized in pediatric research.13,14,26,37

Despite the cross-sectional design of our study, we showed that MF and a score of low-grade inflammation biomarkers are associated with IR parameters in adolescents after adjustments for potential confounders. Adolescents with a high low-grade inflammation and low levels of MF exhibit the highest risk of IR. Moreover, the results of this study suggest that higher levels of MF could to minimize the deleterious effect of inflammation on adolescent’s IR.

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Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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